## REMARKS

The Examiners have rejected the pending claims under 35 U.S.C. 112, second paragraph as continuing to be indefinite in language for expressly stated reasons. In addition, the Examiners have rejected the pending claims under 35 U.S.C. 102(b) as anticipated by International Publication No. WO 96/32129 of Blecha *et al.* In response, applicants have amended independent claims 11 and 15 respectively. By these amendments and the discussion presented hereinafter, applicants believe they have overcome and obviated each basis for rejection stated by the Examiners in this non-final Official Action.

As a preliminary matter, applicants acknowledge and accept with thanks the withdrawing of the basis for objection and each of the multiple bases for rejection made previously for this application. Applicants deeply appreciate the Examiners' continuing attention to these matters.

Applicants will now address each substantive basis for rejection stated by the Examiners in the instant Official Action with respect both to the relevant factual circumstances and the relevant legal requirements. However, because the Examiner's stated views and positions are dependent upon a proper recognition of applicants' invention as defined by

the language of the presently pending claims, applicants deem it both useful and necessary to summarily review the scope and delineation of the subject matter as a whole which is applicants' claimed invention.

## I. Applicants' Claimed Invention

Applicants' invention is defined most broadly by amended independent claims 11 and 15 respectively. These are composition of matter definitions directed to a family of pharmacologically active PR-39 derived oligopeptides.

The wording of presently amended independent claims 11 and 15 restate the commonly shared characteristics and properties of the PR-39 oligopeptide family members and structures described in detail by the Specification text; and these independent claims delineate a pharmacologically active peptide membership which is shorter-length and size-limited, is functionally specific, and is structurally related as a family of unique oligopeptides.

In addition, the commonly shared characteristics and properties of the PR-39 derived oligopeptide family are individually set forth as the requisite elements and specific limitations recited by amended independent claims 11 and 15 respectively. Thus, amended claim 11 (or amended claim 15) requires that each PR-39 derived oligopeptide family

member present not less than six separate and individual traits and attributes. These are:

(1) an oligopeptide which is less than 26 amino acid residues in length (or alternatively is less than 20 amino acid residues in length);

(2) an oligopeptide whose N-terminal amino acid residue sequence begins with Arg-Arg-Arg;

(3) an oligopeptide which is an analog of the amino acid sequence of native PR-39 peptide;

(4) an oligopeptide which is pharmacologically active for selectively altering the proteolytic degradation activity of proteasomes in-situ;

(5) an oligopeptide able to interact in-situ with at least the $\alpha 7$ subunit of such proteasomes as are present within the cytoplasm of a cell; and

(6) an oligopeptide able selectively to alter the proteolytic degradation activity of proteasomes having an interacting $\alpha 7$ subunit such that their proteolytic degradation against a specific peptide becomes selectively inhibited while the proteolytic degradation mediated by said proteasomes apart from against the specific peptide remains unaltered.

Exemplifying and representing the entire PR-39 derived oligopeptide family membership are the short-length peptides recited by dependent claims 12, 13 and 14 respectively. Note that these specific examples

provide oligopeptides which are respectively 15, 11 and 8 amino acid residues in length; and that these short-length oligopeptides, as well as the entire PR-39 derived oligopeptide family membership as a whole, are functional to achieve three separate requisite actions.

These three requisite actions are: that each oligopeptide be pharmacologically active for selectively altering the proteolytic degradation activity of proteasomes in-situ; that at least the $\alpha$7 subunit of the proteasomes interact with the oligopeptide; and that the proteolytic degradation against a specific peptide mediated by these proteasomes with an interacting $\alpha$7 subunit becomes selectively inhibited while the proteolytic degradation apart from against the specific peptide remains unaltered.

With this precise understanding and appreciation of applicants' claimed invention in mind, a pointed review and discussion of each basis for rejection is presented below.

II. The Rejection Under 35 U.S.C. 112, Second Paragraph

The Examiner has rejected pending claims 11-15 as being indefinite for failing to particularly point our and distinctly claim the subject matter which applicants regard as their invention. The

immediate problem is centered on the use of the words "at least one specific peptide" and "other peptides" in the claim language.

With all due respect to the Examiners, the stated reasons as given appear to be an instance of the Examiners' refusal to recognize or accept common wording and phrasing for comparing and distinguishing between different types and kinds of peptides which are typically degraded by the proteasomes of a cell. The Examiners are indulging in a form of semantic gamesmanship; and seem to present a subjective viewpoint with regard to the definiteness of certain words and phrases employed in proper context.

However, it is applicants' desire and intention to advance the substantive prosecution of this application, rather than hinder or prolong it unnecessarily. To achieve this purpose in the most expeditious manner, applicants' have chosen to delete the phrases "at least one" and "against other peptides" entirely from the language recited by independent claims 11 and 15; and added new wording to claims 11 and 15 which more precisely differentiates and distinguishes between the selectively inhibited proteolytic degradation mediated by proteasomes against "a specific peptide" from the proteolytic degradation mediated by proteasomes "apart from against said specific peptide" which remains unaltered. Applicants respectfully submit and maintain that these amendments to the language

of independent claims 11 and 15 respectively resolve and settle this wording issue in its entirety.

Moreover, as regards the language of the presently pending claims as a whole, the first inquiry is to determine whether the claims do, in fact, set out and circumscribe a particular area or subject matter with a reasonable degree of precision and particularity. It is here where the meaning of the language employed to define the invention is analyzed; not in a vacuum, but always with regard to the teachings of the prior art and within the particular use or application disclosed by the Specification as it is understood and interpreted by one possessing ordinary skill in the pertinent art [In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976)].

Applicants note that each of the terms used in the pending claims is well understood; is not subject to numerous meanings and interpretations; and that there is no discrepancy, no confusion, and no ambiguity with regard to the antecedent descriptive basis provided by the Specification text. Rather, the language recited by the pending claims as a whole read on subject matter which is completely described and enabling by the Specification text. Moreover, each of the pending claims is explicit and clearly stated, and sets forth and circumscribes a particular subject matter area with the requisite reasonable degree of precision and particularity [In re Moore, 169 U.S.P.Q. 236 (C.C.P.A. 1971)].

For these reasons, applicants respectfully submit that each and every claim now pending satisfies the requirements of precision, clarity, and particularity required by the second paragraph of 35 U.S.C. 112. Accordingly, applicants respectfully request that the Examiner reconsider her stated position and withdraw this ground of rejection against the presently pending claims.

## III. The Rejection Under 35 U.S.C. 102(b)

The Examiners have rejected claims 11-15 under 35 U.S.C. 102(b) as anticipated by the Blecha et al reference [International Publication No. WO 96/32129]. Applicants note also that this PCT printed publication is identical to and claims the priority of U. S. Patent No. 5,830,993 - a prior art patent and publication which is formally of record and constitutes a substantive part of the prosecution file history for this application.

The Examiners' view is that the Blecha *et al.* publication teaches that native PR-39 and its truncated analogs (such as the PR-14 and PR-19 analogs) inhibit leukocyte superoxide anion production; attract leukocytes; and are medicaments that fight infection at a wound site. On this basis, the Examiners then state that "These truncated analogs of PR-39 have the inherent characteristics and properties of the claimed peptides"... - since they contain amino acid sequences similar to those

recited by pending claims 12-14. The Examiners' reasoning is thus based solely and exclusively upon the legal doctrine of "inherency"; and the Examiners have concluded that the claims of the present application are "inherently anticipated" by the disclosure of the Blecha *et al.* reference. In response, applicants respectfully submit and maintain that the Examiners are legally in error as regards the propriety of their using the inherency doctrine with respect to the issue of novelty; that the Examiners' stated view and position concerning the substance of the Blecha *et al.* publication is inaccurate and is a factual fallacy; and that the Examiners' reliance upon the inherency doctrine is based solely upon a speculative theory which has no factual basis to support it. Applicants will now demonstrate and evidence each of these points.

A. The Proper Legal Requirements And True Limits Of The 'Inherency Doctrine'

Applicants respectfully submit and maintain that the Examiners' rationale and position is centered on an erroneous and distorted interpretation of the legal doctrine of inherency. For this reason, a summary review of the legal doctrine of "inherency" is presented here.

The legal doctrine of "inherency" holds that anticipation (and alternatively obviousness) may be established when a prior art reference

either discloses exactly or suggests overtly the identical goals of a claimed invention; and also provides both the materials and the manner of using the materials to achieve the intended goal as a consequential result.

Unfortunately, the Examiners have failed to recall that the legal doctrine of inherency is available only when the claimed invention can be identified or inferred from the disclosure of the prior art reference with substantial certainty. Probabilities and speculation are not a substitute for substantial certainty; and probabilities and speculation are not legally sufficient grounds upon which to invoke and apply the inherency doctrine [In re Oelrich, 212 U.S.P.Q. 323 (C.C.P.A. 1981); In re Chandler, 117 U.S.P.Q. 361 (C.C.P.A. 1985)].

In order for a claimed invention, such as a composition of matter, to be inherently disclosed - all the requirements recited by each of the component elements comprising the composition as claimed must be the necessary and only reasonable construction to be given to the information disclosed by the prior art reference; and the invention as claimed must inevitably come into existence and be the direct result of what is actually revealed within the prior art disclosure. Equally important, the mere possibility that a certain result or outcome may or might result from the information disclosed by the prior art reference is not legally sufficient to

establish inherency [In re Robertson, 49 U.S.P.Q. 2d 1949 (Fed Cir. 1999)].

The legal obligation and the evidentiary burden to provide such substantial certainty lies solely upon the Examiners. It is the Examiners who must show not only that the prior art reference might offer the result, consequence, property, or trait; but rather must demonstrate with substantial certainty that the prior art disclosure will provide compositions of matter which have the requisite structure, characteristics, and properties as well as are pharmacologically active and functional to achieve the intended result recited by the claimed invention. If, however, the desired consequence or result could only potentially or speculatively occur as a theoretical possibility or contingent event within a circumstantial setting; or when there is no factual basis disclosed which is operative for making the compositions or for effecting the desired outcome, then the reference-disclosed information is factually inadequate and legally insufficient [Continental Can Co., U.S.A. Inc. v. Monsanta Co., 20 U.S.P. Q. 2d 1746 (Fed. Cir. 1991)].

It is therefore well established, as a matter of law, that for a composition of matter having particular structure, properties and pharmacological activities to be deemed as inherently disclosed, it is not sufficient that the ordinary person following the teachings and suggestions

of the prior art disclosure might – by some unknown procedure, process or means – obtain a composition of matter having the desired structure, properties and functional activities. To the contrary, it is legally demanded that identifiable means and knowledge sufficient to make and use the composition of matter and obtain the desired result be in existence and available via the prior art reference. Inherency as a doctrine and the legal basis for rejection cannot be proven or established upon a personal speculation or where reasonable objective doubt exists as to whether or not the necessary knowledge exists [In re Wertheim, 191 U.S.P.Q. 90 (C.C.P.A. 1976)].

B. The Factual Content Of The Blecha *et al.* Publication

In conducting this review of the facts disclosed within this prior art reference, applicants will take special care to point out what the goals and objectives for the disclosed Blecha *et al.* invention are, as explicitly stated within the printed publication; the means and manner in which the Blecha *et al.* invention is said to be functional and operative; and the explicitly imposed limitations and restrictions of the Blecha *et al.* invention as disclosed by the printed publication itself. The Examiners' attention is directed particularly to these points of information as the best evidence and proof of the Examiners' multiple factual errors.

1. The Blecha *et al.* invention is explicitly directed to the synthesis of anti-microbial peptides which can be used for inhibiting microbial growth and microbial infections [Page 1, lines 7-30]. The synthesized anti-microbial peptides are compositions based on the 39 amino acid residue sequence of PR-39 peptide isolated from wound fluid and shown previously to be able to induce syndecan expression on mesenchymal cells [Page 1, lines 34-35; Page 2, lines 1-14].

2. The Blecha *et al.* anti-microbial peptides are analog compounds based upon the known structure of PR-39 peptide, but are truncated peptides which still retain the functional anti-microbial domain of the original PR-39 peptide structure. All of these truncated peptides, however, must retain the demonstrated anti-microbial property of the original PR-39 peptide – that is, the active killing of microorganisms or the active suppression of microbial multiplication and/or growth [Page 3, lines 9-20].

3. The Blecha *et al.* disclosure sets forth a series of in-vitro assays by which to determine empirically which of the synthesized, truncated peptide compounds derived from the original PR-39 structure possess the requisite anti-microbial activity. These assays include: the gel-overlay

assay, the lawn-spotting assay, the minimal inhibitory concentration test, the measurement of post antibiotic effects, the susceptibility of neutrophil phagocytosis, the regulation of neutrophil superoxide anion production, neutrophil chemotaxis capability, and the influence on intestinal epithelial cells [Page 6, lines 16-34; Page 7, lines 1-34; Page 8, lines 1-21].

4. The Blecha *et al.* reference discloses that six truncated analog peptide structures based on the original PR-39 peptide were synthesized, as is shown by Fig. 1 of the publication [Page 5, lines 31-35; Page 6, lines 1-15]. Of these, only three truncated peptide analogs had an amino acid residue sequence which began using the N-terminal end of PR-39, but existed as shorter length peptide structures. These three truncated analog structures are the PR-14, PR-19 and PR-26 peptides. In comparison, the truncated PR-15 peptide structure contained only a portion of the COOH-terminal residues of the original PR-39 peptide sequence; and the truncated PR-16 analog contained only residue Nos. 11-26 in the original PR-39 structure; and the truncated PR-23 analog contained only residue Nos. 4-26 of the original PR-39 peptide sequence. Thus, none of the PR-15, PR-16 or PR-23 truncated peptide analog structures contained an N-terminus sequence beginning with the amino acid resides Arg-Arg-Arg [see SEQ ID NOS: 6, 5 and 3 respectively].

5. The Blecha *et al.* disclosure also states that of the six truncated analog peptide structures synthesized and tested, **only the truncated PR-26 analog structure was found to have any anti-microbial activity in comparison to that of the original PR-39 peptide** [Page 12, lines 18-35; Page 13, lines 1-47]. The experiments and empirical data presented within the reference reveal that only the PR-26 truncated peptide analog demonstrated the required anti-microbial killing properties using the in-vitro assays; and that **the PR-14 and the PR-19 analogs failed to show any anti-microbial activity** [Page 15, lines 27-29].

6. The disclosure of this Blecha *et al.* publication also explicitly states in detail what the direct teachings and implied suggestions of the described invention and the experimental tests and empirical results actually are: These are stated to be [see Page 12, lines 30-35; Page 13, lines 1-4]:

(a) The COOH-terminus of the PR-39 structure does not contribute to antibacterial activity;

(b) The N-terminus of the PR-39 structure is not sufficient for antibacterial activity;

(c) The PR-26 truncated peptide containing residue Nos. 1-26 of the original PR-39 structure is the antibacterial domain; and

(d) A particular secondary peptide structure conformation is required to exist and be present for both the PR-26 truncated analog peptide and the original PR-39 original peptide in order that antibacterial activity exists

7. The Blecha *et al.* disclosure explicitly states that **the one and only truncated analog peptide structure demonstrably functional for its intended purpose and goal is the PR-26 truncated analog peptide**. Of all six truncated analog peptides synthesized and experimentally tested, only the PR-26 peptide analog alone is said to be suitable for the stated goal and purpose of anti-microbial activity via its demonstrated antibacterial properties [Page 13, lines 5-25].

In sum, the Blecha *et al.* publication is markedly different and radically remote from applicants' claimed invention. The explicitly stated differences and distinctions include:

(a) The absolute requirement by the Blecha *et al.* reference that any truncated analog peptide structure derived from the original PR-39 peptide must demonstrate potent anti-microbial properties and effects;

(b) The Blecha *et al.* stated view that no set of characteristics, traits or properties other than a potent and effective antibacterial activity is of any value or is of interest for any purpose;

(c) The experimentally proven fact of the Blecha *et al.* disclosure that of all the six truncated peptide analogs synthesized and experimentally evaluated, only one – the PR-26 analog having 26 amino acid residues - was found to be biologically active or operative for its intended goal and purpose, anti-microbial activity; and

(d) The view of the Blecha *et al.* disclosure that no similar peptide structure and no truncated analog of the original PR-39 peptide less than 26 residues in length is either biochemically active or useful.

Applicants wish to make their stance entirely clear and understood. It is applicants' position that the Examiners' use of and reliance upon the inherency doctrine fails to meet the necessary minimal legal requirements because of the factual deficiencies and insufficiencies set forth above. Therefore, the inherency doctrine may not be properly employed as a basis and rationale for rejection because - the body of evidence employed by the Examiners as the underlying factual basis for rejection is purely speculative and can only be characterized as a self-serving theory not having any realistic probability as such. Applicants' position is amply

demonstrated and fully supported by the absence of relevant supporting facts, information, knowledge, or data within the single cited and applied reference, the Blecha *et al.* publication.

Given this deficiency of facts and lack of evidentiary support for the Examiners' stated views, a summary review of the appropriate and proper legal standards concerning anticipation is in order.

C. The Proper Legal Standards For Determining Novelty

As a matter of long established law, anticipation under 35 U.S.C. 102(b) requires exact identity of the claimed process or claimed composition within a conventionally known method or procedure existing previously in the prior art. The claimed composition (or the claimed process), including each component element constituting the invention as a whole, must be described or embodied, directly or indirectly, within a single reference.

Anticipation thus requires exact identity or effective duplication of applicant's claimed invention; and the single reference of record must describe applicant's claimed invention sufficiently and in detail such that a person of ordinary skill in that field has possession of the invention itself. Also, in deciding the issue of anticipation, the Examiners must identify each requisite element as recited within the claims; determine their

meaning in light of the Specification; and identify the existence and presence for each of the corresponding elements as being disclosed in the allegedly anticipating reference [Scripts Clinical and Research Foundation vs. Genentech Inc., 18 U.S.P.Q. 2d 1001 (Fed. Cir. 1991); Glaverbel Society Anonyme vs. Northlake Marketing and Supply Inc., 35 U.S.P.Q. 2d 1496 (Fed. Cir. 1995)].

It is useful here also to identify the legal basis and standard for obviousness under 35 U.S.C. 103. Where applicant's claimed subject matter can be rejected as obvious in view of a single reference or a combination of prior art references, a proper analysis must consider inter alia two factors: 1) whether the prior art of record would have suggested to those of ordinary skill in the art that they should carry out the claimed process or make the claimed composition; and 2) whether the prior art would also have revealed that in so carrying out or making, those of ordinary skill would have a reasonable expectation of success [In re Dow Chemical Company, 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988)]. Both the suggestion and the reasonable expectation of success must be found within the prior art references(s) themselves and not in applicant's disclosure [In re Vaeck, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991)]. In addition, the same inquiry must be carried out in the context of a purported "obvious modification" of the prior art information. The mere

fact that the prior art might be modified in the manner suggested by an Examiner does not make that modification obvious unless the prior art suggested the desirability of the modification [In re Fritch, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992) and the references cited therein].

Applicants therefore respectively affirm and submit that the Examiners' stated views and conclusions in the instant Official Action have failed to conform to the legal standard and requirements for anticipation (as well as for obviousness).

D. The Lack Of Relevance For The Blecha *et al.* Publication

As regards the Blecha *et al.* reference, which the Examiner erroneously believes provides support for an inherency rejection, attention is directed to the facts actually disclosed by the publication itself as exemplifying what the Examiners have unfortunately overlooked and ignored. The Blecha *et al.* publication reveals only such facts as:

(1) The sole criteria of use for the described truncated peptide analogs is exclusively as anti-microbial agents. No other activity, property, or characteristic is revealed or suggested.

(2) Only one synthesized truncated peptide analog of 26 amino acid residue length was empirically found to be biochemically active for its intended purpose. All other the synthesized truncated peptide analogs

shorter than 26 residues in length had no anti-microbial activity and thus had no utility as such.

(3) The presence of an antibacterial domain as a distinct moeity is required in order for the requisite antibacterial activity to exist within the truncated peptide analog; and only the original PR-39 peptide and the truncated PR-26 peptide analog encompassed the requisite antibacterial domain within their structures.

(4) The mechanism for biological activity is specified and required in order that the 26 residue length peptide analog structure be functional for its intended purpose. Thus, the specified means and limited manner of interaction for a peptide analog having the requisite antibacterial domain is an essential part of the truncated peptide analog structure; and any peptide sequence of any length which is devoid of the required antibacterial domain cannot and is not functional or useful for the stated purpose and goal - the killing of microbes and the inhibition of microbial growth and infections.

These are explicit, direct and unrelenting requirements for the Blecha *et al.* truncated peptide analogs as well as for the limited utility and function recognized for the PR-26 analog peptide. Thus, the Examiners have clearly failed to recognize that there is no information, no facts, and no suggestion whatsoever within the Blecha *et al.* reference for

using any truncated peptide analog for any purpose except as an antimicrobial agent. The entire mechanism of action described and the whole of the Blecha *et al.* disclosure is specified and compulsory for a peptide analog capable of antibacterial inhibition and antimicrobial killing capability, as stated by the description of this reference.

Applicants therefore affirm and maintain that the Blecha *et al.* publication of record does not teach and could not suggest to those of ordinary skill in the art that they should make or employ the oligopeptide compositions defined by claims 11-15. Moreover, the Blecha *et al.* reference of record has also revealed that, even if the ordinary practitioner had thought of making or practicing applicants' claimed invention, those of ordinary skill in this field would not have any reasonable expectation of success. Applicants further maintain and submit that there is nothing inherent or intrinsic in the cited and applied Blecha *et al.* publication of record which offers or provides a basis for any expectation which would render the subject matter of independent claims 11 and 15 respectively as being either implied or foreseeable. Accordingly, applicants' subject matter as a whole defined by claims 11-15 is a family of compositions which are novel and have substantial patentable merit.

E. The Examiners' Erroneous Conclusions

For all of the reasons presented above, applicants thus find the Examiners' stated views and conclusions to be factually inaccurate and legally erroneous with respect to applicants' claimed invention. The Examiners' stated reasons for using the "inherency doctrine" and the requisite factual underpinnings necessary before employing the "inherency doctrine" have been shown to be unsupportable, unjustified and erroneous in their entirety.

It is equally evident that, in an attempt to impose their stated views and positions, the Examiners have acted subjectively, wrongly and prejudicially. The Examiners have unfortunately ignored the sum and substance of the facts disclosed by the Blecha *et al.* publication. In a similar manner, the Examiners have disregarded and evaded from the controlling legal authority of the long-established caselaw decisions which deny and refute the Examiner's expressed reasons and views regarding inherency. Ample evidence demonstrating each of these prejudicial factual and legal errors has been presented in detail herein.

In addition, the Examiners have acknowledged that the cited and applied Blecha *et al.* publication does not explicitly or directly disclose those particular compositions of matter having the attributes, properties and capabilities defined by claims 11-15. Instead, the entirety of the

Examiner's reasoning is based solely on the doctrine of inherency – a position which is not factually or legally acceptable in these circumstances.

For all the reasons stated herein, applicants respectfully affirm that multiple errors of fact and law have been made by the Examiners; and that, accordingly, independent claims 11 and 15 are therefore allowable as presently defined.

Claims 12-14 depend from independent claims 11 or 15; and merely provide particular limitations and preferred embodiments to the unique and non-obvious invention defined therein. Since independent claims 11 and 15 are believed to be in condition for allowance, and claims 12-14 respectively depend there from, these dependent claims are also believed to be allowable.

In view of the above discussion and detailed analysis of the many factual and legal errors presented by the Examiners, applicants believe that this case is now in condition for allowance and reconsideration is respectfully requested. The Examiners are invited to call applicants' undersigned attorney should she feel that such a telephone call would further the prosecution of the present application.

Respectfully submitted.

MICHAEL SIMONS
YOUHE GAO

Date: May 7, 2003 By: David Prashker

David Prashker
Registration Number 29,693
Attorney for applicants
P.O. Box 5387
Magnolia, Massachusetts 01930
Tel: (978) 525-3794